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20350	7590 10/17/2003		EXAMINER	
TOWNSEND AND TOWNSEND AND CREW, LLP TWO EMBARCADERO CENTER EIGHTH FLOOR SAN FRANCISCO, CA 94111-3834			GOLDBERG, JEANINE ANNE	
			ART UNIT	PAPER NUMBER
			1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

		A. D. Markette				
	Application No.	Applicant(s)				
Office Action Supercont	09/944,951	DENNIS ET AL.				
Office Action Summary	Examiner	Art Unit				
The MAR BIO DATE of the control of	Jeanine A Goldberg	1634				
The MAILING DATE of this communication app Period for Reply	bears on the cover sheet with the (	correspondence address				
A SHORTENED STATUTORY PERIOD FOR REPL THE MAILING DATE OF THIS COMMUNICATION.  - Extensions of time may be available under the provisions of 37 CFR 1.1 after SIX (6) MONTHS from the mailing date of this communication.  - If the period for reply specified above is less than thirty (30) days, a repl - If NO period for reply is specified above, the maximum statutory period - Failure to reply within the set or extended period for reply will, by statute - Any reply received by the Office later than three months after the mailing earned patent term adjustment. See 37 CFR 1.704(b).  Status	136(a). In no event, however, may a reply be the law within the statutory minimum of thirty (30) day will apply and will expire SIX (6) MONTHS from a, cause the application to become ABANDONE	mely filed  ys will be considered timely. If the mailing date of this communication. ED (35 U.S.C. § 133).				
1) Responsive to communication(s) filed on 16.	July 2003 .					
2a)⊠ This action is <b>FINAL</b> . 2b)□ Th	nis action is non-final.					
3) Since this application is in condition for allows closed in accordance with the practice under						
Disposition of Claims	_					
4) Claim(s) 1-33 is/are pending in the application.						
4a) Of the above claim(s) is/are withdrawn from consideration.						
5) Claim(s) is/are allowed.						
6)⊠ Claim(s) <u>1-5,8-24 and 26-33</u> is/are rejected.						
7) Claim(s) <u>6,7 and 25</u> is/are objected to.						
8) Claim(s) are subject to restriction and/o	or election requirement.					
9) The specification is objected to by the Examine	er.					
10) ☐ The drawing(s) filed on is/are: a) ☐ acce		miner.				
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).						
11) The proposed drawing correction filed on is: a) approved b) disapproved by the Examiner.						
If approved, corrected drawings are required in reply to this Office action.						
12)☐ The oath or declaration is objected to by the Examiner.						
Priority under 35 U.S.C. §§ 119 and 120						
13) Acknowledgment is made of a claim for foreign	n priority under 35 U.S.C. § 119(a	a)-(d) or (f).				
a) ☐ All b) ☐ Some * c) ☐ None of:						
1. Certified copies of the priority document	ts have been received.					
2. Certified copies of the priority document	ts have been received in Applicat	ion No				
3. Copies of the certified copies of the prio application from the International Bu * See the attached detailed Office action for a list	ıreau (PCT Rule 17.2(a)).	-				
14) Acknowledgment is made of a claim for domest	•					
a) The translation of the foreign language pro						
Attachment(s)						
1) Notice of References Cited (PTO-892) 2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 3) Information Disclosure Statement(s) (PTO-1449) Paper No(s)	5) Notice of Informal	y (PTO-413) Paper No(s) Patent Application (PTO-152)				

Application/Control Number: 09/944,951 Page 2

Art Unit: 1634

#### **DETAILED ACTION**

1. This action is in response to the papers filed July 16, 2003. Currently, claims 1-38 are pending. Claims 34-38 have been withdrawn as drawn to non-elected subject matter.

- 2. Applicant's have indicated that Claim 9 is withdrawn. However, Claim 9 has not been withdrawn by the examiner. As noted below, the examiner believes that the claim is a duplicate claim.
- 3. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.
- 4. Any objections and rejections not reiterated below are hereby withdrawn.

### Maintained Rejections

# Claim Objections

5. Claim 9 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 9 and Claim 2 are essentially the same claim. Claim 2 requires a "difference in DNA methylation" whereas Claim 9 requires "DNA methylation difference." It is unclear how Claim 9 further limits Claim 2.

#### **Response to Arguments**

The response traverses the rejection. The response asserts Claim 9 has been withdrawn. This argument has been reviewed but is not convincing because as stated above, the examiner does not believe that Claim 9 further limits Claim 2. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Thus for the reasons above and those already of record, the rejection is maintained.

# Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
- (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
- 6. Claims 1, 3-5, 8, 14-20, 24, 27, 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Lo et al. (WO 98/39474, September 11, 1998) and rejected under 35 U.S.C. 102(e) as being anticipated by Lo et al. (US Pat. 6,258,540, July 10, 2001.

It is noted that the disclosure of both of the documents is identical. The page numbers refers to the WO document.

The instant specification defines "epigenetic differences" as "any molecular or structural difference other than the primary nucleotide sequence" (page 10, lines 4-6).

Lo et al. (herein referred to as Lo-WO) teaches a method of non-invasive prenatal diagnosis including sex determination and detection of pre-eclampsia in a mother. The prenatal method of Lo-WO differentiates DNA species from a mother and a fetus in maternal serum or plasma by determining epigenetic differences between the DNA species from the mother and the fetus (limitations of Claim 1). The epigenetic differences taught to be detectable in maternal serum and plasma includes detection of chromosomal aneuploidies such as Down's Syndrome (page 5), and elevated concentration of fetal DNA in pre-eclampsia (page 5-6). In Example 1, Lo-WO provides an analysis of fetal DNA for sex determination (page 6). Maternal peripheral blood was collected, centrifuged and the plasma and serum were removed (page 7)(limitations of Claim 3). Lo-WO teaches performing a PCR reaction with Y-specific primers. Lo-WO teaches that non of the 13 women bearing female fetuses and none of the non-pregnant female controls resulted in a positive Y signal when either plasma, serum or cellular DNA was amplified, indicating the accuracy of the technique (page 9)(limitations of claim 4, 5, 14, 24, 27, 33). Example 2 demonstrates a quantitative analysis of fetal DNA in maternal serum in aneuploid pregnancies (page 14). Real time quantitative SYR PCR was performed on serum DNA extracted from women bearing aneuploid and normal fetuses (page 14) and for pre-eclamptic and control patients (page 22). The results demonstrated that the concentration of fetal DNA in maternal serum is elevated in aneuploid pregnancies (page 14) and in pre-eclamptic compared with non-preArt Unit: 1634

eclamptic pregnancies (page 22)(limitations of claims 8, 15-20). Therefore, since Lo-WO teaches every limitation of the claims, Lo-WO anticipates the claimed invention.

### **Response to Arguments**

The response traverses the rejection. The response asserts that detection of the Y chromosome is not an epigenetic difference. This argument has been reviewed and found convincing, as the primers are designed to detect the primary structure of the Y-chromosomes.

The response asserts that DNA concentration is not "a molecular or structural difference other than the primary nucleic acid sequence." This argument has been reviewed but is not convincing because the broad definition in the specification does not appear to exclude DNA concentration as a molecular difference. Increased quantities of a nucleic acid sequence would not be a difference in primary nucleic acid sequence, but rather a molecular difference. Increased molecules of nucleic acid would constitute a molecular difference. Thus for the reasons above and those already of record, the rejection is maintained.

7. Claims 1-2, 4-5, 9-11, 13, 21-23, 27-29, 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuboto et al (Nature Genetics, Vol. 16, pages 16-17, May 1997).

Kuboto et al. (herein referred to as Kuboto) teaches a methylation-specific PCR method which simplifies imprinting analysis. Kuboto teaches that genomic imprinting plays an important role in Prader-Willi syndrome (PWS) and Angelman syndrome (AS). There is differential methylation between the maternal homologue and the paternal

paternal homologue is unmethylated and transcriptionally active (page 16, col. 1).

homologue such that the maternal homologue is methylated and inactive while the

Kuboto teaches a methylation-specific PCR assay for the detection of PWS and AS

using DNA treated with sodium bisulphate, which converts cytosine to uracil except

when cytosine is methylated (page 16, col. 1)(limitations of claims 10). After treatment

of the genomic DNA with bisulfite CpG dunucleotides are methylated in over 96% of the

maternal chromosome, whereas none are methylated on the paternal chromosome.

PCR primers were designed to amplify the region. Normal individuals showed both a

174-bp PCR product and a 100-b PCR product; PWS patients showed only the 174-bp

product; and AS patients only showed 100-bp PCR product (limitations of claims 1, 2, 9,

11, 13, 27-29, 33). Thus, Kuboto teaches a method of differentiating DNA species from

different individuals in a biological sample, namely blood, amniotic fluid or chorionic

villus, by determining epigenetic differences, namely methylation, between the DNA

species (page 17, col. 1)(limitations of claims 4, 5). Therefore, since Kuboto teaches

every limitation of the claims, Kuboto anticipates the claimed invention.

#### Response to Arguments

The response traverses the rejection. The response asserts that Kubota "shows an affected individual lacks either a 100-bp PCR product (PWS) or a 17-bp PCR product (AS) present in a normal individual." The response argues that the genes are taken from the same individual, not a method for determining differing methylation patterns between DNA species from different individuals. This argument has been reviewed but is not convincing because the individual of interest provides a sample

which allows differentiation of DNA nucleic acids which originated from different individuals, namely their mother and father. Thus, the sample contains DNA species from different individuals, as required by the instant claims.

The response asserts that Kubota does not describe differentiating DNA species from different individuals. This argument has been thoroughly reviewed, but is not found persuasive because the nucleic acids were differentiated using methylation. The maternal and paternal nucleic acids were DNA species which originated from different individuals, namely the mother and father of the individual.

Thus for the reasons above and those already of record, the rejection is maintained.

# Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
- 8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

Art Unit: 1634

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kuboto et al (Nature Genetics, Vol. 16, pages 16-17, May 1997) in view of Herman et al. (PNAS, Vol. 93, pages 9821-9826, September 1996).

Kuboto et al. (herein referred to as Kuboto) teaches a methylation-specific PCR method which simplifies imprinting analysis. Kuboto teaches that genomic imprinting plays an important role in Prader-Willi syndrome (PWS) and Angelman syndrome (AS). There is differential methylation between the maternal homologue and the paternal homologue such that the maternal homologue is methylated and inactive while the paternal homologue is unmethylated and transcriptionally active (page 16, col. 1). Kuboto teaches a methylation-specific PCR assay for the detection of PWS and AS using DNA treated with sodium bisulphate, which converts cytosine to uracil except when cytosine is methylated (page 16, col. 1)(limitations of claims 10). After treatment of the genomic DNA with bisulfite CpG dunucleotides are methylated in over 96% of the maternal chromosome, whereas none are methylated on the paternal chromosome. PCR primers were designed to amplify the region. Normal individuals showed both a 174-bp PCR product and a 100-b PCR product; PWS patients showed only the 174-bp product; and AS patients only showed 100-bp PCR product (limitations of claims 1, 2, 9, 11, 13, 27-29, 33). Thus, Kuboto teaches a method of differentiating DNA species from different individuals in a biological sample, namely blood, amniotic fluid or chorionic

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Art Unit: 1634

villus, by determining epigenetic differences, namely methylation, between the DNA species (page 17, col. 1)(limitations of claims 4, 5).

Kuboto does not specifically teach sequencing DNA to detect a DNA methylation difference.

However, Herman teaches that following chemical modification of cytosine to uracil by bisulfite treatment, the altered DNA may be amplified and sequenced to provide detailed information within the amplified region of the methylation status of all CpG sites. Herman specifically states that "the only technique that can provide more direct analysis then MSP for most CpG sites within a defined region is genomic sequencing" (page 9825, col. 2).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have sequenced the nucleic acid of the small nuclear ribonucleoprotein-associated polypeptide, taught by Kuboto to be differentially methylated, to determine the methylation status of the nucleic acid in an individual. The ordinary artisan would have clearly recognized that the method of sequencing the nucleic acid would have been an equivalent means of determining the methylation status of the region. The method of sequencing the entire region provides detailed information within the amplified region of the methylation status of all of the CpG sites. While the method of methylation-specific PCR may have its advantages, sequencing the entire amplified regions provides a very clear detailed analysis of each of the CpG sites within the nucleic acid. Herman states that "the only technique that can provide more direct analysis then MSP for most CpG sites within a defined region is genomic

Art Unit: 1634

sequencing" (page 9825, col. 2). With this very clear detailed analysis, the ordinary artisan will be able to determine whether certain CpG sites are essential to a specific diagnosis. Therefore, depending on the information desired by the ordinary artisan, the ordinary artisan may choose to perform the methylation detection assay using either the methylation specific PCR method or a more detailed sequencing analysis of the entire region.

# **Response to Arguments**

The response traverses the rejection. The arguments directed to Kubo are discussed above.

The response asserts that Herman teaches DNA sequencing is inferior to MSP. This argument has been reviewed but is not convincing because while Herman points out the benefits of MSP, the method of sequencing is the most direct means for analysis. While MSP may have certain benefits, sequencing also has certain benefits. Depending on the preference of the artisan, the ordinary artisan would have been motivated to have chosen sequencing in cases where a more detailed sequence analysis of the entire region may be evaluated.

There response argues that the DNA sequencing is an inferiour analysis to MSP and thus, there is no motivation to combine. This argument has been thoroughly reviewed, but not found convincing because the skilled artisan would have to weigh the two methods' advantages to determine which of the advantages are more desirable. The mere existence of some disadvantages of sequencing would not preclude the ordinary artisan from evaluating and weighing the benefits and disadvantages to

4004

Art Unit: 1634

determine which method of analysis is preferable. For the artisans preferring a detailed analysis of the entire region, they would select a method of sequencing.

Thus for the reasons above and those already of record, the rejection is maintained.

10. Claims 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuboto et al (Nature Genetics, Vol. 16, pages 16-17, May 1997) in view of Nuovo et al. (PNAS, Vol. 96, No. 22, pages 12754-12759, October 26, 1999).

Kuboto et al. (herein referred to as Kuboto) teaches a methylation-specific PCR method which simplifies imprinting analysis. Kuboto teaches that genomic imprinting plays an important role in Prader-Willi syndrome (PWS) and Angelman syndrome (AS). There is differential methylation between the maternal homologue and the paternal homologue such that the maternal homologue is methylated and inactive while the paternal homologue is unmethylated and transcriptionally active (page 16, col. 1). Kuboto teaches a methylation-specific PCR assay for the detection of PWS and AS using DNA treated with sodium bisulphate, which converts cytosine to uracil except when cytosine is methylated (page 16, col. 1)(limitations of claims 10). After treatment of the genomic DNA with bisulfite CpG dunucleotides are methylated in over 96% of the maternal chromosome, whereas none are methylated on the paternal chromosome. PCR primers were designed to amplify the region. Normal individuals showed both a 174-bp PCR product and a 100-b PCR product; PWS patients showed only the 174-bp product; and AS patients only showed 100-bp PCR product (limitations of claims 1, 2, 9,

Art Unit: 1634

11, 13, 27-29, 33). Thus, Kuboto teaches a method of differentiating DNA species from different individuals in a biological sample, namely blood, amniotic fluid or chorionic villus, by determining epigenetic differences, namely methylation, between the DNA species (page 17, col. 1)(limitations of claims 4, 5).

Kuboto does not specifically teach using methylation specific polymerase chain reaction (PCR) in situ to detect methylation.

However, Nuovo et al. (herein referred to as Nuovo) teaches in situ detection of methylation using an in situ methylation-specific PCR. Nuovo teaches that hypermethylation is associated with loss of expression of one copy in the normal settings of inactivation of the female X chromosome and the silenced alleles for paternally imprinted gene (page 12754, col. 1). Nuovo teaches that the methods of genomic sequence to assess cytosine methylation does cannot easily address critical issues such as the precise timing of DNA methylation changes in specific cell types during embryonic development (page 12754, col. 1). Nuovo teaches a method of using MSP-ISH (methylation-specific PCR in situ) for tracing the evolution of cell populations harboring hypermethylation associated inactivation (page 12754, col. 2).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have modified and improved the method of Kuboto which analyzes DNA from women who are pregnant to detect the presence of PWS and AS. The ordinary artisan would have recognized based upon the teachings of Nuovo that analysis of cells provides the increased benefit By modifying the method of Kuboto to analyze cells will provide additional information regarding the precise timing of DNA

methylation and changes in specific cell types during embryonic development as suggested by Nuovo. In order to further analyze and study the inactivation of the female X chromosome and imprinting, the ordinary artisan would be motivated to determine the temporal methylation to further study and analyze the PWS and AS disorders.

## Response to Arguments

The response traverses the rejection. The arguments directed to Kubo are discussed above.

The response asserts that there is no motivation to combine. The response asserts that the proposed modification defeats the stated goal. This argument has been reviewed but is not convincing because the stated goal of Kubota may be to dtect imprinting analysis. The modification of Nuovo, while potentially more time consuming, the modification would have the advantage of tracing the evolution of cell populations which contain methylation associated inactivation which is suggested by Nuovo explicitly. Benefits of modification need not be less time consuming, as seemingly suggested by the response. The benefits may be increased information, such as information regarding the temporal evolution of cell populations.

Thus for the reasons above and those already of record, the rejection is maintained.

### **Double Patenting**

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

Art Unit: 1634

and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 1, 3-5, 8, 14-20, 24, 27, 33 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-7, 12-25 of U.S. Patent No. 6,258,540.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by or would have been obvious over, the reference claim(s). See e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentable distinct from each other because Claim 1, 3-5, 8, 14-20, 24, 27, 33 of the instant application is generic to all that is recited in Claim 1-7, 12-25 of U.S. Patent No. 6,258,540. That is, Claim 1-7, 12-25 of 6,258,540 falls entirely within the scope of Claim 1, 3-5, 8, 14-20, 24, 27, 33, or in other words, Claim 1, 3-5, 8, 14-20, 24, 27, 33 are anticipated by Claim 1-7, 12-25 of 6,258,540. Here, claim 1 of U.S. Patent No. 6,258,540 recites a method

for detecting paternally inherited nucleic acids of fetal origin performed on maternal serum or plasma by detecting the presence of a paternally inherited nucleic acid.

Page 15

### Response to Arguments

The response traverses the rejection. The response asserts that detection of the Y chromosome is not an epigenetic difference. This argument has been reviewed and found convincing, as the primers are designed to detect the primary structure of the Ychromosomes.

The response asserts that DNA concentration is not "a molecular or structural difference other than the primary nucleic acid sequence." This argument has been reviewed but is not convincing because the broad definition in the specification does not appear to exclude DNA concentration as a molecular difference. Increased quantities of a nucleic acid sequence would not be a difference in primary nucleic acid sequence, but rather a molecular difference. Increased molecules of nucleic acid would constitute a molecular difference. Thus for the reasons above and those already of record, the rejection is maintained.

#### Conclusion

- 12. Claims 6, 7, 25 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
- 13. Claims 1-5, 8-24, 26-33 are rejected over the art.
- 14. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg October 7, 2003

> Supervisory Patent Examiner Technology Center 1600